REMARKS/ARGUMENTS

Claims 1-7, 17-22, and 25-28 are currently pending in the application.

Claims 17 and 18, drawn to methods for loading one through-hole array from an adjacent through-hole array, stand rejected under 35 U.S.C. §112, second paragraph, for indefiniteness, and, as understood, stand reject as anticipated by de Macario, as do claims 21 and 22.

Claim 25, drawn to a method for diffusing light in a novel optical diffuser formed of liquid-filled microchannels, stands rejected as anticipated by Davis and also as anticipated by de Macario.

Claims 27-28, both drawn to methods for mixing liquids by bringing together pairs of perforated platens, both stand rejected as anticipated by de Macario.

Claims 1 and 7 stand rejected over de Macario in view of Cole. These claims are drawn to creating a concentration gradient across a set of containers by differential diffusion during the course of contacting the containers with a liquid.

Claims 19-20 and 26 stand rejected over de Macario in view of Davis, while claim 26 stands rejected additionally on grounds of obvious-type double patenting.

The issued status of a parent application referenced in paragraph [0001] has been corrected. Applicant thanks the Examiner for calling attention to that point.

Entry of amendments of claims 1, 17, and 25, in order to place these claims in condition for allowance or consideration on appeal, is requested. It is hoped that characterization of the second liquid in claim 1 as a *single* liquid will clarify that differing concentrations of a solute are not introduced into the various containers serially, and that the phrase "unimpeded by any solid structure" in claim 17 will clarify that, by aligning the through-holes of respective platens, a column is formed in space that may be filled by

a liquid, bridging gaps where necessary. Finally, amendment of claim 25, while not changing the scope of the claim, clarifies that, for use as a light diffuser to generate a uniform field of light, multiple through-holes are illuminated simultaneously.

Differential Diffusion Creating a Concentration Gradient

Claims 1 and 7 relate to a method whereby the containers of an integral structure, having already been filled with a first liquid, are then filled

· by *contact* with a second liquid (the *same* second liquid contacting each of the containers)

· such that the degree of diffusion of a specific substance varies with position among the containers, thereby creating a gradient of that substance with respect to position of the container within the structure.

Cole (US Patent No. 4,110,165, at Example 42, in col. 37, taken as a typical example; other procedures described by Cole are equivalent in this regard) describes the effect of incubating trays containing bacteria that are held in separate wells. The wells are characterized by gradients with respect to the concentrations of various inhibitors of bacterial growth. But there is no discussion of how the concentration gradients are achieved, presumably by standard methods of dilution and then pipetting into the respective wells. There is certainly no teaching in Cole that the concentration gradients might be achieved by the methods of differential diffusion taught and claimed in accordance with the embodiments of the present invention claimed in claims 1-7.

To clarify that the gradient is achieved, in accordance with the claimed invention, by contacting each container with the same liquid, addition of the single word 'single' is requested, though no change of scope of the claim is intended thereby.

De Macario does not teach any formation of gradients whatsoever, and thus does not provide the teaching of the claimed invention that is absent in Cole. Claims 1-7 should thus be in condition for allowance.

Stacking

Claims 17-20 are drawn to methods for loading a liquid into a plurality of through-holes. The region of space including the volumes of co-aligned through-holes and any intervening air (as shown below) constitutes a continuous "column" (a prolate volume). As filed, claim 17 recited a "continuous channel", but it was acknowledged that the meaning of "channel" might require material sides for the entire length of the space denoted as a channel. This is not the case for the term "column", as currently recited in the claim. Addition of the words "unimpeded by any solid structure" is requested for the sake of additional clarity. It is believed that any indefiniteness in claims 17 and 18 has been overcome.

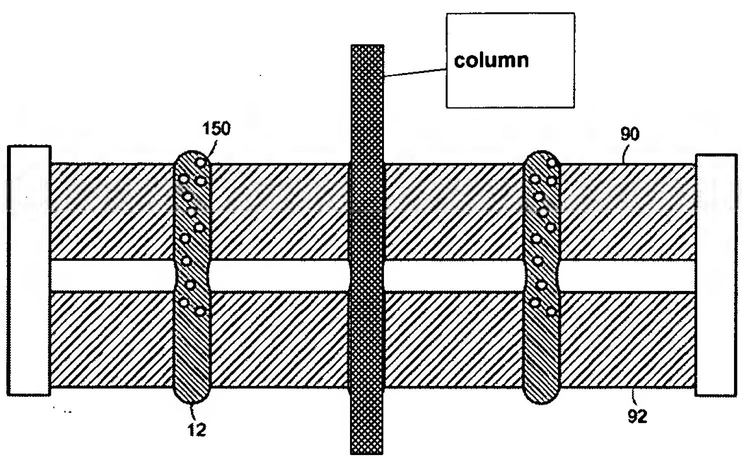


FIG. 16

A method for loading multiple through-hole arrays at once is described in par. [101] of the Application. Par. [104] teaches: "The volume of liquid withdrawn into each syringe preferably equals the volume of liquid in a column of aligned through-holes in the array stack."

There is no teaching in de Macario that relates to loading a liquid into a plurality of stacked through-holes by virtue of their stacking since the through-holes of de Macario are already loaded. De Macario states:

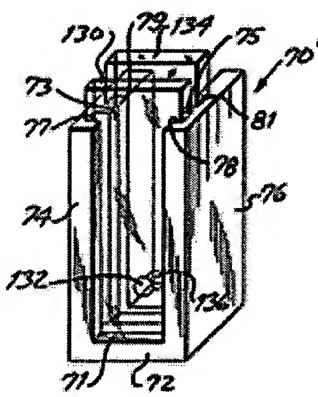
> The small separation between plates **130** and **134** enables the liquid sample placed on retaining element **132** (or on retaining element **136**) or on retaining element **132´**, to form a liquid bridge suspended

> between the retaining elements of the adjacent plates. (De Macario, col. 10, lines 32-36)

Thus, according to de Macario (col. 10, lines 32-36), each of the holes ('retaining elements') is filled separately, then, while it is unclear how that serves 'to form a liquid bridge,' the plates are inserted into parallel vertical slots.

The following is the figure shown by de Macario in connection with the foregoing discussion cited in the Office Action. There is no teaching here that through-holes might be aligned, nor of how any 'liquid bridge' might be formed without sliding plates with respect to one another as the plates, filled with liquids of positive (convex) meniscus, are inserted into guide slots **77, 78, 79** thereby causing smearing of the contents of the respective through-holes. (If the liquid contents exhibit a negative (concave) meniscus, then a 'liquid bridge' could not be formed.)

FIG.8



In any event, the claimed method step of transferring a liquid from outside the stack to form a continuous column is not suggested by de Macario. Thus, none of claims 17 and the claims dependent therefrom, claims 18-20, can have been be anticipated by de Macario. Nor does Davis provide the missing the teaching, thus each of claims 17-20 is patentable over de Macario, alone or in combination with Davis.

Mixing

Claims 21, 22, 27 and 28 are drawn to a method of mixing liquids contained in two platens by stacking them to allow diffusion between connecting through-holes, as depicted, for example, in Fig. 16 shown above. De Macario talks about adding reagents to the contents of his "retaining elements." But he teaches performing such addition by adding reagents and samples *separately* to the holes of a single platen (in the discussion bridging columns 10-11). There is no suggestion in de Macario of any parallelism that might be achieved by aligning corresponding holes, and there is no suggestion of diffusion of material from one through-hole to another. Nor does Davis supply the missing teaching, thus claims 21, 22, 27, and 28 are patentable over de Macario and Davis, alone or in combination.

Diffusion of Light by an Array of Liquid Microlenses

Claim 25, drawn to an optical diffuser formed of liquid-filled microchannels, stands rejected as anticipated by Davis. There is certainly no teaching in Davis of a method for creating uniform illumination over an area. Davis describes, exclusively, interrogating the contents of individual holes. A diffuser, as well known in the optical arts, provides a substantially Lambertian emission profile with angle (See, for example, Born & Wolf, "Principles of Optics," Cambridge University Press, (1999), p. 195, attached.) The present application teaches:

> Water **270** in the capillaries forms a set of microlenses which serve to diffuse light from light source **272** across the array and thus provide a uniform illumination field for optical analysis. The use of liquid microlens arrays, generally, is within the scope of the present invention.

There is no teaching or suggestion in any reference of record to illuminate a plurality of liquid-filled microchannels to this end. Claim 25 should therefore be allowable.

Perforated Platen Permitting Retention of Distinct Samples

Claim 26 may profitably be compared with claim 1 of US Patent No. 6,743,633, a patent issued from a divisional of the parent application (USSN 09/225,583) of the present continuation-in-part application. Claim 1 of Hunter '633 reads as follows:

1. A method for analyzing specified properties of a set of samples, the method comprising:

a. providing a platen having two substantially parallel planar surfaces, an inner layer of hydrophilic material, two outer layers of hydrophobic material coupled to opposite sides of the inner layer, and a two-dimensional array of a plurality of addressable through-holes, the through-holes being disposed substantially perpendicularly to the planar surfaces and the array characterized by an areal density of at least 1.6 through-holes per square millimeter;

b. loading a first sample into a first set of through-holes of the two-dimensional array, the first sample being a liquid;

c. retaining the first sample in the first set of through-holes by surface tension;

d. adding a second sample into a specified subset of through-holes, the specified subset of through-holes having at least one adjacent through-hole containing a sample other than the second sample, the specified subset of through-holes further coinciding with one of the first set of at least one of the though-holes thereby permitting a reaction between the first sample and the second sample, wherein the layers of hydrophobic material prevent capillary outmigration of the samples; and

e. characterizing the reaction in the specified subset of through-holes in terms of the specified properties.

Claim 1 of Hunter '633 was allowed over Davis recognizing that the Davis device is directed toward being filled with a single liquid and supporting a single liquid, such that outmigration of liquid and crosstalk among neighboring mesh holes is of no concern in the teaching of Davis.

Whether a particular pore of a mesh of the sort taught by Davis would hold a sample distinct from that of a neighboring hole is neither addressed by Davis nor readily answerable by application of methods known in the art. Whether there are notoriously well-known devices that would transfer a liquid to a single pore of, say, a screendoor, is not of record in the case. Therefore, the teaching of geometries that enable the invention as claimed in claim 26 are patentable over Davis, as well as over the combination of Davis with de Macario, since there is no suggestion to combine these references, Davis being directed to support of a single liquid sample.

Finally, a terminal disclaimer is attached to overcome the obviousness-type double-patenting rejection of claim 26 with respect to a claim which issued from its parent application.

If the Examiner has any outstanding questions, he is invited to call Applicants' undersigned representative at 617-443-9292.

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intensity, at the point (ξ, η) in the direction (α, β). It must be distinguished from the visual sensation of brightness, from which it will in general differ, because the eye is not equally sensitive to all colours;* this point will be discussed more fully later.

δF is usually decomposed in two different ways, to show the explicit dependence on $\delta\Omega$ and δS:

$$\delta F = \delta I \delta\Omega = \delta E \delta S. \tag{3}$$

Comparison of (1) and (3) gives

$$\delta I = \frac{\delta F}{\delta\Omega} = B\cos\theta\delta S, \tag{4}$$

$$\delta E = \frac{\delta F}{\delta S} = B\cos\theta\delta\Omega. \tag{5}$$

The integral

$$I(\alpha, \beta) = \int B\cos\theta \,\mathrm{d}S \tag{6}$$

taken over a piece of surface is called the *radiant intensity*† *in the direction* (α, β), and the integral

$$E(\xi, \eta) = \int B\cos\theta \,\mathrm{d}\Omega \tag{7}$$

taken throughout a solid angle is called the *radiometric illumination at the point* (ξ, η).

The variation of B with direction will depend on the nature of the surface, especially on whether it is rough or smooth, whether it is self-luminous, or whether it transmits or reflects other light. Often it is permissible to assume that, to a good approximation, B is independent of the direction. The radiation is then said to be *isotropic*. If the radiation is isotropic and if the radiating surface is plane, (6) reduces to

$$I(\alpha, \beta) = I_0\cos\theta, \tag{8}$$

where

$$I_0 = \int B \,\mathrm{d}S.$$

The photometric intensity in any direction then varies as the cosine of the angle between that direction and the normal to the surface. Eq. (8) is known as *Lambert's* (*cosine*) *law*, and when satisfied one speaks of *diffuse emission* or *diffuse reflection*, according to whether the surface is emitting or reflecting.

The measurement of the quantities F, B, I and E involves the determination of a

* One often uses the adjective 'photometric' when one wishes to stress that a particular quantity is evaluated with regard to its visual, rather than its true physical effects.

† In Chapter I the light intensity was defined as the time average of the amount of energy which crosses per second a unit area perpendicular to the direction of the flow. This quantity must not be confused with the *radiant* intensity as defined by (6). It is unfortunate that the same word is used to denote two different quantities. Except in the present section we shall always understand by 'intensity' the quantity introduced in Chapter I. If the surface element δS at P is orthogonal to the Poynting vector, the intensity (in the sense of Chapter I) is equal to the illumination δE at P.

Principles of optics

Electromagnetic theory of propagation, interference and diffraction of light

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